Origins of . . .

Familial cancer: histopathological perspectives

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Familial cancer is a large topic spanning fields of study within multiple hierarchical levels including genes, cells, tissues, organs, affected subjects, affected families, and populations. It fits into no single clinical discipline, but requires input from multiple specialties within medicine and surgery, as well as oncology, paediatrics, clinical genetics, and pathology. Familial cancer also falls within the domains of public health and cancer prevention, and raises cultural, ethical, psychological, and educational issues of considerable complexity. This account explores only the histopathological contribution to our understanding of familial cancer, recognising that this input has been considerable in both scale and importance.

Central to histopathology is the universally acknowledged value of a tissue diagnosis that defines the mechanism underlying a pathological process. If the mechanism is neoplasia, the lesion is classified according to histogenetic type using a set of variables giving an indication of grade as well as the extent of spread or stage. This exercise provides the baseline for all further correlations, whether clinical, molecular or a combination. The fine splitting of morphological subtypes may be demonstrated many years later to be associated with specific molecular findings. Such correlations could not have been made without the pre-existing histopathological descriptions.

Mention should be made of two further features of histopathological practice. Long before the advent of modern information technology, retrospective access to patient records was made possible through the establishment of coded disease indices and patient indices. This comprehensive cross referencing system has underpinned the entire enterprise of pathologically based clinical research over the past century. Furthermore, the system allowed access not only to slides but also to formalin fixed, paraffin wax embedded tissue blocks. The stored DNA, spanning periods of five or more decades, has opened research possibilities that would have been only dimly perceived when the original material was retained in laboratory files.

Histopathological recognition of familial cancer

Histopathologists do not usually interact directly with patients or their families, therefore, they are not placed in an ideal position to recognise familial cancer. The histopathological contribution is more to the detailed characteri-

sation of a syndrome, particularly when the syndrome is uncommon, produces changes in internal organs, and is associated with disparate lesions that are not obviously connected. The pathologist may also distinguish features that are relevant to pathogenesis, diagnosis, and clinical behaviour. Incisive contributions to the recognition of familial cancer syndromes have included the examples of multiple endocrine neoplasia type II (MEN II) and the Beckwith-Wiedemann syndrome. In the case of MEN II, the association of thyroid carcinoma with pheochromocytoma had been noted in isolated case reports spanning 30 years, but it was Williams¹ in 1965 who documented the medullary or C cell nature of the thyroid neoplasm. Despite the occurrence of parathyroid tumours in MEN types I and II, Williams recognised the distinction of the two syndromes, the bilaterality of pheochromocytoma, the familiarity of the condition, and considered the neuroendocrine basis of the syndrome¹ that was subsequently given the term MEN II.² Williams and Pollock³ later described the additional manifestations of neuromas of the oral mucosa and diffuse ganglioneuromatosis affecting the myenteric plexus of the gastrointestinal tract (designated later as MEN IIb or III). The MEN II features are now being correlated with mutations in the cytoplasmic domain (tyrosine kinase signalling) of the ret proto-oncogene.^{4,5}

Systematic necropsy practice allows seemingly unrelated observations to be grouped into a single syndrome when the same pattern is repeated in several subjects. In 1969, Beckwith⁶ assembled the features of macroglossia, omphalocele, adrenal cytomegaly, gigantism, and hyperplastic visceromegaly (necropsy findings presented initially in 1963) and linked these with the observations of familiarity made by Wiedemann⁷ to derive the Beckwith-Wiedemann syndrome, which also incorporated tumours of childhood, notably Wilms's tumour or nephroblastoma.⁸

Histopathological contributions to hereditary colorectal cancer syndromes

Cuthbert Dukes was director of the first registry for familial adenomatous polyposis, based in the pathology department at St Mark's Hospital in London. He defined three principal landmarks in the story of polyposis: the recognition of polyposis as a separate disease, the recognition of familial predisposition, and the relation of polyposis to colorectal carcinoma.⁹

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He emphasised the distinction between polyposis and "pseudopolyposis" secondary to ulcerative colitis, and the importance of distinguishing polyposis from "isolated adenomatous polyps of children or adults" and from the "crop of minute adenomatous proliferations which often surround early cancers of the rectum and colon". Morson¹⁰ subsequently reclassified lesions that Dukes had termed adenomas as hamartomatous juvenile polyps (adenomatous polyps of children) and metaplastic polyps (minute adenomatous proliferations). Morson's contribution was to recognise the neoplastic and precancerous nature of a subset of epithelial polyps for which he retained the earlier generic term adenoma. This established the adenoma-carcinoma concept as the evolutionary paradigm for colorectal cancer. The neoplastic nature of adenomas has now been confirmed by the demonstration of clonality and mutations of oncogenes (K-ras) and tumour suppressor genes (for example, APC).¹¹

In 1959 Turcot and colleagues described two teenaged siblings with malignant tumours of the brain and colorectum, and moderate numbers of colorectal adenomas.¹² This appeared to be distinct from familial adenomatous polyposis and subsequent reports generated confusion over the mode of inheritance. Hamilton *et al*¹³ investigated 15 families with Turcot's syndrome including the original Turcot family. Germline APC mutations were detected in 10 families in which 11 of the 14 brain tumours were medulloblastomas. In the families without APC mutations the brain tumours were glioblastoma multiforme, and in two families germline mutations of DNA mismatch repair genes (hMLH1 and hPMS2) were detected. Germline DNA was not available from the Turcot family, but a glioblastoma multiforme and a colorectal adenoma showed DNA microsatellite instability. The original Turcot family was almost certainly an example of hereditary non-polyposis colorectal cancer (HNPCC). Turcot's syndrome is unlikely to exist as an entity, but encompasses families with familial adenomatous polyposis and HNPCC. This example illustrates how a meticulous approach combining histopathology with molecular genetics can successfully overturn misconceptions promulgated over 40 years. It also highlights the benefit of retaining tissues (in this case the original Turcot samples were stored in hospital laboratories in Quebec for 40 years following the initial publication).

As the pathology of HNPCC differs in only subtle ways from common bowel cancer, one would not have anticipated the discipline of anatomical pathology to have been instrumental in its recognition. The pride of place of familial adenomatous polyposis as the paradigm of hereditary colorectal cancer dampened belief in HNPCC as an entity. For example, it was held that adenomas could be inherited either as an autosomal dominant trait (familial polyposis) or as an autosomal recessive trait giving rise to sporadic adenomas and familial clustering of colorectal cancer as a consequence of the adenoma-carcinoma sequence.¹⁴

HNPCC with its lack of premonitory lesions and autosomal dominant pattern of inheritance did not fit with such a model.

The first documented family with HNPCC was Aldred Warthin's "family G".¹⁵ Warthin served as a pathologist at the University of Michigan Medical Centre, being Professor of Pathology and Director of the Pathological Laboratories from 1903 till his death in 1931. He emphasised the importance of linking precise histopathological diagnosis and family history and conducted his research on material that was representative of the general population of the State of Michigan. His message relating to the inaccuracy of death certification in clinical research remains valid today.¹⁶ Based on a survey of 1000 evaluable cases, Warthin found that 15% had a positive family history and among these were several large pedigrees, including family G. Following Warthin's early documentation of a typical HNPCC family, it was the perspicacity of the physician Henry Lynch^{17,18} that gave credibility to a concept that failed to find widespread acceptance until the genetic basis was proven by linkage and positional cloning (requiring DNA extraction from archival tissue) and led to the characterisation of the causative DNA mismatch repair genes.¹⁹⁻²²

The contribution of anatomical pathology came also in the demonstration of pathogenetic mechanisms. While the frequency and anatomical distribution of adenomas in HNPCC differed little from adenomas in the general population (based on a necropsy series), HNPCC adenomas were shown to occur in contiguity with early cancers and to display aggressive features in the form of size, grade, and villosity.²³ This suggested that the mutator effect was more evident at the step of adenoma progression than initiation. Without adenoma initiation, subsequent neoplastic evolution cannot occur. This opened the possibility of cancer control through dietary or chemopreventive blockade of the early steps of neoplasia.

Histopathology has also helped to define light microscopic characteristics of both HNPCC cancers and non-familial cancers displaying the unstable microsatellite phenotype. No feature is specific but two patterns are over represented: mucinous cancers (including the signet ring variety), and poorly differentiated cancers. In the latter, large cells are grouped into nests, trabeculae or sheets with little or no evidence of glandular differentiation. These tumours are relatively well circumscribed and associated with peritumoral and tumour infiltrating lymphocytes.²⁴ However, the existence of such a tumour pattern with a good prognosis that belied the lack of glandular differentiation had been recognised previously.²⁵

Genetic explanations for histopathological variation in familial tumours

There is a long histopathological tradition of splitting tumours into groups based on differing morphological patterns. This has clinical importance when particular histopathological

types are shown to differ in their aetiology, epidemiology, prognosis or response to treatment. The advent of molecular genetics meant that correlations could be made at the molecular-morphological level. It had already been noted that the pattern of large cell undifferentiated colorectal carcinoma²⁵ was over represented in HNPCC. The not dissimilar pattern of medullary or atypical medullary carcinoma was also over represented among breast cancers developing in women carrying a BRCA1 germline mutation.²⁶ Hereditary renal cell carcinoma may occur as the classic clear cell variant when the underlying mutation implicates the von Hippel-Lindau (VHL) gene.²⁷ A subset of hereditary renal cancers showed similar multiplicity and bilaterality, yet was not linked to the VHL gene. This was distinguished histopathologically by a papillary architecture. The syndrome of hereditary papillary renal carcinoma (HPRC) has recently been assigned to the MET proto-oncogene. Germline mutations of the tyrosine kinase domain of MET were identified in affected members of HPRC families.²⁸

The preceding examples show how prior histopathological classifications may define subsets of tumours with links to specific genes and thereby assist with the ultimate cloning of those genes or allow correct assignment of genes to specific hereditary syndromes. Awareness of these associations facilitates the histopathological diagnosis of hereditary tumours.

Future of histopathology in the field of familial cancer

Although familial cancer is a multidisciplinary problem, the contribution of histopathology to research and clinical practice has often been seminal and this has been illustrated with respect to selected syndromes. Yet, at a time when familial cancer is beginning to gain recognition as a health problem of considerable magnitude, histopathology is losing its place as a major force in modern medicine. The cause of this has been the divorce of experimental and clinical pathology. The former has essentially disappeared within the wider arena of biomedical research. The latter is gradually being transferred from its role as a central pillar of medical practice to a support service operating along the lines of a business unit. To remain competitive anatomical pathology must become cheap and fast with its focus shifting from the needs of the patient to the needs of the clinician (not necessarily equivalent to the actual needs of the patient). Yet, histopathology has previously been a slow and careful discipline, engaging the needs of the patient to the latest advances in medical knowledge, and seeking to add to that knowledge in the process.

To convert histopathology into a commercial enterprise would destroy much of its purpose, as clinical research, sharing of clinical data, and retention of specimens generate costs rather than profit. Unless the traditional values and activities associated with histopathology are fostered, the discipline will cease to

underpin research and practice in the field of familial cancer and further progress in the area may be limited. Histopathology is not a spent discipline. Given the examples cited in this overview it is clear that disease classifications will continue to change, new diagnostic criteria will be developed, and new familial syndromes will be recognised. A month before he died, Warthin wrote: "Pathology is not to my mind a separate subject to be taught academically, but one underlying and intimately connected with all the clinical subjects of the curriculum; the correlation of pathology with the clinical picture represents to my mind the highest function of medical teaching."²⁹ This message remains vital and true nearly 70 years on.

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